

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 14

III. REMARKS

Applicant respectfully requests that this application be reconsidered in view of the above amendments and the following remarks.

1. Status of the Claims

Claim 1-29 are currently pending in this application. New Claims 30-34 have been added in this amendment. Therefore, Claims 1-34 are now pending for examination on the merits.

2. Summary of the Amendments

Claim 1 has been amended to delete the term "suitable" at each occurrence. Similar amendments have been made in Claims 5, 16 and 25.

Additionally, Claim 1 has been amended to insert "the method" before "comprising"; and to insert the designations "(a), (b) and (c)" before each of the steps of the method. Similar amendments have been made in Claims 16 and 25.

Claim 6 has been amended to delete "or" before "dioxane."

Claim 7 has been amended to replace the abbreviation "DMF" with "N,N-dimethylformamide"; and to delete "or" before "methanol."

Claims 11 and 12 have been amended to recite that "the reaction mixture is acidified with..." instead of "the acid is...."

Claim 15 has been placed in independent form.

Claim 16 has been amended as described above and also by deleting an obvious and inadvertent typographical error. Specifically, the second occurrence of "R³ is" has been deleted.

New Claims 30-34 have been added. Support for Claim 30 is found, for example, on page 3, lines 20-25 and page 35, line 04 to page 36, line 19; for Claim 31, on page 4, line 02; for Claim 32, on page 4, lines 25-26; for Claim 33, page 5, line 04; and for Claim 34, page 5, lines 07-09.

These amendments are being made to more clearly define and distinctly claim the subject

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 15

matter Applicant regards as the invention. No new matter is introduced by these amendments.
Entry of these amendments is respectfully requested.

3. Objections to the Specification

The Examiner has objected to the specification because of a typographical error. Specifically, the Examiner has indicated that the word "allyl" on page 36, line 26, appears to be intended to read "alkyl." In response, Applicant respectfully notes that the term "allyl" was intended to be used at this location. Accordingly, this objection to the specification may be withdrawn.

4. Objections to the Claims

Claim 15 has been objected to under 35 U.S.C. §1.75(c), as being in improper dependent form for allegedly failing to further limit the subject matter of a previous claim. Specifically, the Examiner has indicated that the method of Claim 1 is directed to alkylating a glycopeptide while the method of Claim 15 is directed to isolating a glycopeptide. In response, Applicant has rewritten Claim 15 to be in independent form. Therefore, this objection may be withdrawn.

Claim 6 and 7 have been objected to because the abbreviation "DMF" allegedly does not have antecedent basis. Specifically, Claim 6 recites "N,N-dimethylformamide" whereas Claim 7, which depends from Claim 6, uses the abbreviation "DMF". In response, Claim 7 has been amended to replace the abbreviation "DMF" with the term "N,N-dimethylformamide". Accordingly, this objection may be withdrawn.

Additionally, Claim 16 has been objected to because of a typographical error. Specifically, the phrase "R³ is" was inadvertently repeated twice in this claim. In response, Applicant has amended Claim 16 to deleted the second occurrence of the phrase "R³ is". Therefore, this objection may be withdrawn.

In the view of the above amendments, Applicant respectfully requests that the objections to the claims be withdrawn.

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 16

5. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 3, 4, 6, 7 and 9 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Examiner has indicated that the term “about” as used in Claims 3, 4 and 9 is a relative term which allegedly renders the claims indefinite. Applicant respectfully traverses this rejection for the following reasons.

Earlier this year, the Court of Appeals for the Federal Circuit held that using the term “about” with a numerical figure is not indefinite because one of ordinary skill in the art would understand that “about” was intended to encompass the range of experimental error that occurs in any measurement. *BJ Servs. Co. v. Halliburton Energy Servs. Inc.*, 67 U.S.P.Q.2d 1692 (Fed. Cir. 2003). In the present case, Applicant has used the term “about” when defining the ratio of alkylation on the saccharide-amine relative to other amino groups. Specifically, in Claims 3 and 4, Applicant recites that the ratio is “at least about 10:1” and “at least about 20:1,” respectively. One skilled in the art would understand how measure this ratio (for example, using the HPLC procedures disclosed by Applicant in Examples 2 and 3) and would also understand that the term “about” is intended to encompass the range of experimental error that occurs with any such measurement (such as HPLC). As a result, one skilled in the art would understand whether any given value is within or outside the scope of the Applicant’s claims. Accordingly, Claims 3 and 4 are not indefinite.

Similarly, Claim 9 recites “a temperature range of about 0°C to about 50°C.” Once again, one skilled in the art would understand how measure temperature (for example, using a thermometer) and would also understand that the term “about” is intended to encompass the range of experimental error that occurs when measuring temperature. As a result, one skilled in the art would understand whether any given value is within or outside the scope of the Applicant’s claim and therefore, Claim 9 is also not indefinite. Accordingly, since the term “about” as used in Claims 3, 4 and 9 is not indefinite, Applicant respectfully requests that this rejection be withdrawn.

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 17

The Examiner has also indicated that the use of "or" before "dioxane" in Claim 6 and before "methanol" in Claim 7 renders these claims confusing. In response, Applicants have amended Claim 6 to delete "or" before "dioxane"; and Claim 7, to delete "or" before "methanol". Accordingly, this rejection may be withdrawn.

Additionally, the Examiner has indicated that there is allegedly insufficient antecedent basis for the term "the acid" in Claim 11. In response, Applicants have amended Claim 11 to recite "wherein the reaction mixture is acidified with a carboxylic acid or a mineral acid." Therefore, this rejection can be withdrawn.

Finally, the Examiner has indicated that the term "suitable base" as used in Claims 1 and 16 is not clear. In response, Applicants have amended Claims 1 and 16 to delete the term "suitable". Accordingly, this rejection can be withdrawn.

In view of the above amendments, Applicants respectfully request that the rejection of Claims 3, 4, 6, 7 and 9 under 35 U.S.C. §112, second paragraph, be withdrawn.

6. Rejections Under 35 U.S.C. §102

Claims 1-29 have been rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 5,998,581, to Richard Berglund et al. For the following reasons, this rejection is respectfully traversed.

Anticipation under 35 U.S.C. §102 requires that each and every element of the claimed invention be disclosed in a prior art reference. A prior art reference that merely discloses similar but not identical elements is insufficient to anticipate the claimed invention.

In the present case, Applicant's presently claimed invention is not anticipated by the Berglund reference because the Berglund reference does not teach each and every element of Applicant's method. Specifically, the Berglund reference does not teach (a) combining a glycopeptide with an aldehyde or ketone and a base; (b) acidifying the resulting reaction mixture; and then (c) combining the reaction mixture with a reducing agent.

By way of background, many glycopeptides typically have two or more basic amino groups and, when preparing semi-synthetic derivatives of such glycopeptides, it is often desirable

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 18

to react the glycopeptide regioselectively to provide alkylation at one amino group in preference to another. The Berglund reference teaches that such regioselectivity can be achieved by using a source of copper to provide a soluble copper complex of the glycopeptide, which is then reductively alkylated (see, for example, column 9, line 64 to column 10, line 19).

In contrast, Applicant has discovered that a high degree of regioselectivity can be achieved in the absence of copper by controlling the order of addition of the reactants and pH of the reaction mixture. Specifically, Applicant's method includes first reacting a glycopeptide having an amino-saccharide group with an aldehyde or ketone in the presence of a base; and then acidifying the reaction mixture with an acid. Finally, a reducing agent is added to afford the glycopeptide alkylated at the amino group of the amino-saccharide. Without intending to be limited in any way by theory, Applicant believes that during the first step an imine and/or hemiaminal intermediate is formed by reaction of the glycopeptide with the aldehyde or ketone. Upon acidification of the reaction mixture, less stable imines and/or hemiaminal intermediates are hydrolyzed (i.e., those formed at the amino groups other than the amino-saccharide group) so that upon addition of the reducing agent, the regioselectivity of the alkylation reaction is significantly improved for alkylation at the amino group of the amino-saccharide.

Turning now to the Berglund reference, this document does not teach or suggest the particular reaction conditions presently claimed by Applicant. For example, in most of the examples of this reference, the aldehyde and reducing agent are added at the same time to the reaction mixture. (See, for example, Examples 2-19 beginning in column 19, at line 29). In Example 1 (column 12, line 08), the reducing agent was added after the aldehyde was combined with the glycopeptide, but this example does not teach or suggest conducting the reaction first under basic conditions and then under acidic conditions before addition of the reducing agent.

Accordingly, since the Berglund reference does not teach each and every element of Applicant's presently claimed method, Applicant respectfully requests that the rejection of Claims 1-29 under 35 U.S.C. §102(e) be withdrawn.

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 19

7. Rejections Under 35 U.S.C. §103

Claims 27-29 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,998,581, to Richard Berglund et al., in view of U.S. Patent No. 4,698,327, to Ramakrishnan Nagarajan et al. For the following reasons, this rejection is respectfully traversed.

Claims 27-29 are not obvious in view of the Berglund and Nagarajan references because these reference, either alone or when combined, do not provide any motivation to modify the teachings of the references to produce Applicant's presently claimed invention. Moreover, even if the cited references provided sufficient motivation to establish a *prima facie* case of obviousness, Applicant's specification provides surprising and unexpected results which are sufficient to rebut such a *prima facie* case of obviousness.

More specifically, Claims 27-29 depend directly or indirectly from Claim 1 and therefore, the issue to be decided is whether the method of Claim 1 and the additional steps defined by Claims 27-29 are obvious in view of the cited references. To establish a *prima facie* case of obviousness, among other requirements, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine reference teachings in a manner that produces the claimed invention.

In the present case, the Examiner has given no reason why or how one skilled in the art would modify the teachings of the Berglund or Nagarajan references, or combine the teachings of these references, to arrive at Applicant's presently claimed invention. As previously indicated, Applicants invention requires a specific order of addition of the reactants and control of the pH of the reaction mixture. These aspects of the presently claimed invention are neither taught nor suggested by the cited references.

Moreover, assuming for the sake of argument that the cited references provide sufficient motivation to establish a *prima facie* case of obviousness, it is well established that a *prima facie* case of obviousness can be rebutted by evidence showing that the claimed subject matter possesses a superior or unexpected property. In the present case, Applicant's specification provides data that illustrate that the presently claimed invention possesses a superior and

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 20

unexpected property. Specifically, in Example 2 beginning on page 41, line 20, the alkylation process conducted according to the present invention afforded the following results (reproduced with annotation from page 42, lines 08-15):

Elution Time (min)	Area % by RV-HPLC	Product
2.0	15	Vancomycin (starting material)
3.2	77	Title Compound (alkylated on amino-saccharide)
3.3	3	Unidentified
3.4	0.5	Alkylation on <i>N</i> -methyl leucine
4.0	0.8	Alkylation on both vancosamine (amino-saccharide) and <i>N</i> -methyl leucine
4.1	0.4	Unidentified

In contrast, when the reaction was conducted by adding the reducing agent and then acidifying the reaction mixture, the following results were obtained (reproduced with annotation from page 43, lines 07-15):

Elution Time (min)	Area % by RV-HPLC	Product
2.0	29	Vancomycin (starting material)
3.2	50	Title Compound (alkylated on amino-saccharide)
3.3	2	Unidentified
3.4	7	Alkylation on <i>N</i> -methyl leucine
4.0	13	Alkylation on both vancosamine (amino-saccharide) and <i>N</i> -methyl leucine
4.1	0.5	Unidentified

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 21

Comparison of these data demonstrate that the presently claimed method provides a product mixture with a significantly higher percentage of the compound resulting from alkylation at the amino-saccharide group (77% vs. 50%), and a lower percentage of the compounds resulting from alkylation at the *N*-methyl leucine position (0.5% vs. 7%), or from bis-alkylation (0.8% vs. 13%). Such results are surprising and unexpected especially, for example, in view of the teachings of the Berglund reference that copper is required to achieved improved regioselectivity. Accordingly, even if the Examiner was able to establish a *prima facie* case of obviousness based on the cited references, these surprising and unexpected results, which are neither taught nor suggested by the cited references, are sufficient to rebut such a *prima facie* case of obviousness.

In summary, the method of Claim 1 is not obvious in view of the Berglund and Nagarajan references because these reference, either alone or when combined, do not provide any motivation to modify the teachings of the references to produce Applicant's presently claimed invention. Moreover, even if the cited references provided sufficient motivation to establish a *prima facie* case of obviousness, Applicant's specification provides surprising and unexpected results which are sufficient to rebut such a *prima facie* case of obviousness. Since Claims 27-29 depend from Claim 1 and add further steps to Claim 1, these claims are also not obvious in view of the cited references. Accordingly, Applicant respectfully maintains that the rejection of Claims 27-29 under 35 U.S.C. §103(a) is in error and therefore, withdrawal of this rejection is respectfully requested.

8. Request for a Telephone Interview

In order to engage in reasonable efforts to conclude prosecution of this application, Applicant respectfully requests a telephone interview with the Examiner and the Supervisor Examiner having signature authority for this application to discuss any issues that are not resolved by the submission of this response. Should there be any remaining issues, the Examiner is respectfully requested to telephone the undersigned attorney at (650) 808-6406 to schedule a mutually convenient time for the interview.

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 22


Consideration of the above amendments and remarks is respectfully requested.
Applicants believe this application is now in condition for allowance and a notice to that effect is respectfully requested. Should there be any questions concerning this response, the Examiner is requested to telephone the undersigned attorney at (650) 808-6406.

Respectfully submitted,

THERAVANCE, INC.

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